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A Case of Atypical McCune–Albright Syndrome Requiring Optic Nerve Decompression

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McCune–Albright syndrome (MAS) is a disease of noninheritable, genetic origin defined by the triad of café-au-lait pigmentation of the skin, precocious puberty, and polyostotic fibrous dysplasia. This syndrome, which affects young girls primarily, has also been reported with other endocrinopathies, and rarely with acromegaly and hyperprolactinemia. The fibrous dysplasia in MAS is of the polyostotic type and, apart from the characteristic sites such as the proximal aspects of the femur and the pelvis, the craniofacial region is frequently involved. A male patient with MAS presented with juvenile gigantism, precocious puberty, pituitary adenoma-secreting growth hormone and prolactin, hypothalamic pituitary gonadal and thyroid dysfunction, and polyostotic fibrous dysplasia causing optic nerve compression. Visual deterioration and its surgical management are presented.

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McCune–Albright syndrome (MAS) is a disease of noninheritable, genetic origin defined by the triad of café-au-lait pigmentation of the skin, precocious puberty, and polyostotic fibrous dysplasia.[1,2] The diagnosis of MAS requires the presence of two parts of the triad.[3,4] This syndrome also has been reported with other endocrinopathies, including hyperthyroidism[5,6]; hyperparathyroidism[7]; hypercortisolism[8,9]; acromegaly[10,11]; hyperprolactinemia[12,13]; adenomas of the pituitary,[14,15] thyroid,[16] parathyroid,[7] and adrenal glands[8,9]; vitamin D-resistant rickets[17,18]; and hypothalamic hypogonadotropic hypogonadism.[19] An activating missense mutation in the gene coding for the α-subunit of the Gs protein—Gsα, which causes overproduction of cyclic adenosine monophosphate (cAMP)—has been identified.[20,21] This is believed to be responsible for the abnormalities and mosaicism observed in several affected tissues in MAS by causing increased cell proliferation, inappropriate cell differentiation, and unregulated endocrine secretion.[22,23]

Although, MAS can affect both sexes, the majority of cases have occurred in young girls. However, precocious puberty due to autonomous testicular hyperfunction are occasionally seen in boys. Apart from the consequences of the disease itself, young women appear to be at an increased risk for developing breast cancer, possibly due in part to the prolonged estrogen stimulus or to the presence of a mutation in the breast tissue itself.[24] On the other hand, malignant change is reported to occur in some patients with fibrous dysplasia and is greatest in young boys with polyostotic disease.[25,26] There is also an increased risk for thyroid and osseous malignancies.[24]

The bone lesions are of the polyostotic type and occur mainly in the proximal femur and pelvis. Craniofacial fibrous dysplasia occurs in 50% to 100% of patients. It involves most frequently in descending order the maxilla; mandible; and frontal, sphenoidal, ethmoidal, parietal, temporal, and occipital bones.[27,28] Bone lesions are commonly described as the substitution of normal bone by an immature, disorganized fibrochondro-osseous tissue due to an overgrowth of primitive bone-forming cells causing woven ossified tissue, increased bone matrix formation, and extensive marrow fibrosis.[23] Although fibrous dysplasia is a benign lesion, after radiation treatment malignant change to mainly sarcomas occurs in 0.4%[29] and in 4% of MAS patients.[30]

Other manifestations include bone pain, pathological fractures, and leg length discrepancies. In the craniofacial region, painless bony enlargement causing facial disfigurement is the usual

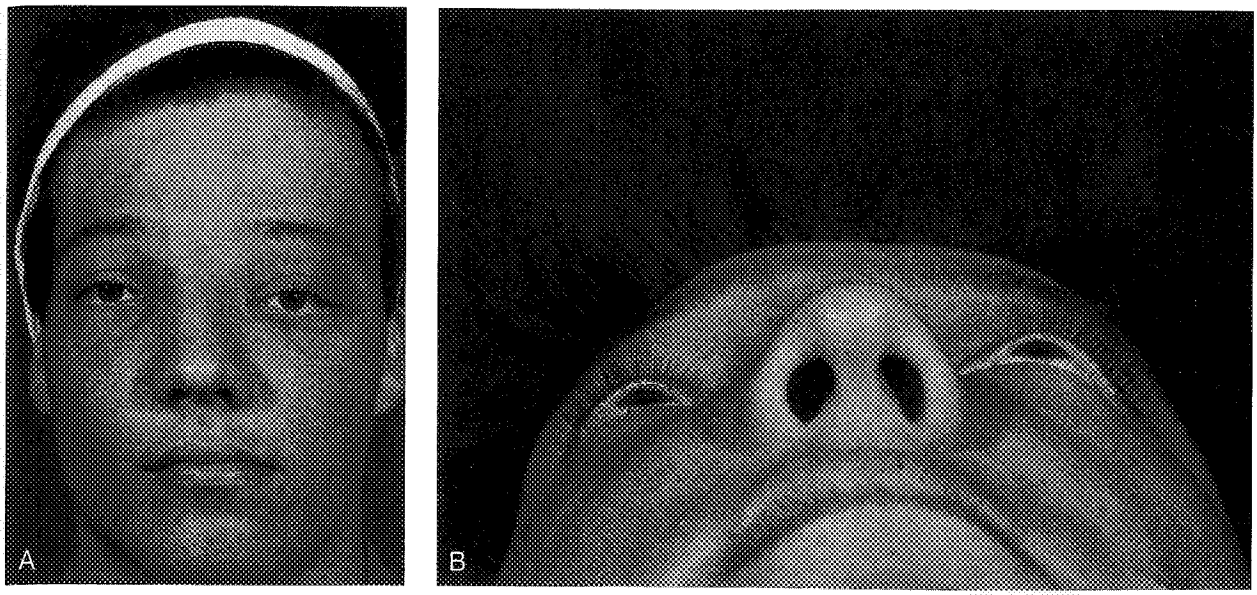

Fig 1. (A, B) A 17-year-old boy with coarse facial features, and asymmetry and prominence of the left orbit.

symptom. Because the nasal fossae, paranasal sinuses, internal auditory canals, or orbits are involved, there may be functional disturbances such as sinus infections, hearing impairment, proptosis, lateral and inferior globe displacement, diplopia, restrictive ocular mobility, pain, epiphora, decreased visual fields, and blindness.[31]

Radiological features can be cystic, sclerotic, and mixed or pagetoid. The mixed form occurs in more than half the patients showing the coexistence of radiodense and radiolucent areas. Fibrous replacement of the medullary cavity typically produces a well-defined radiolucent area that can vary from completely radiolucent to a homogenous ground-glass density, depending on the amount of fibrous or osseous tissue. Irregular bands of sclerosis may cross the cystlike lesion to give a multilocular appearance. The bone is often expanded locally and the cortex may be eroded within, predisposing to pathological fracture.[32] The radiological features and clinical presentation are characteristic, but definitive diagnosis requires histological confirmation.

Of all the hormonal abnormalities described in MAS, juvenile gigantism with growth hormone-secreting pituitary adenoma may be the least common type,[33,34] and its treatment is particularly difficult because skull involvement frequently prevents neurosurgical excision, and radiation therapy may cause sarcomatous transformation of dysplastic bone.[35,36]

Patient Report

A 17-year-old boy was first seen in early childhood for gigantism. At age 7 he sustained a right-arm fracture after minor trauma, and a left fibular biopsy revealed a diagnosis of polyostotic fibrous dysplasia. Octreotide and bromocriptine therapy were started in increasing doses. During the past 10 years he had several surgeries on both his hips and arms to reconstruct multiple fractures and to correct leg length discrepancy. At 14 years he developed involvement of the craniofacial region and since then has undergone three surgeries, which consist of shaving involved orbital areas.

On examination at age 17 his height was 195 cm and his weight was 99.7 kg. He had coarse facial features without café au lait pigmentation on his body. He had general fibrous dysplastic involvement of his left face. The left orbit was more prominent than the right and the left eye was protruded (Fig 1). Laboratory studies showed elevated serum prolactin (140 ng per milliliter; reference interval, <10 ng per milliliter), growth hormone (29.1 ng per milliliter; reference interval, <5.0 ng per milliliter), and insulinlike growth factor (999 ng per milliliter; reference interval, 182–780 ng per milliliter). The oral glucose tolerance test showed a paradoxical rise of plasma growth hormone concentration. Plasma concentration of free testosterone was low at 6.4

pg per milliliter with an almost undetectable luteinizing hormone level of 0.7 mIU per milliliter (reference interval, 3–18 mIU per milliliter). Tyrotropin (thyroid stimulating hormone) was low at 0.28 μU per milliliter (reference interval, <10 μU per milliliter), and free T4 was 0.73 μU per milliliter. Alkaline phosphatase was elevated to 480 mM per liter (reference interval, <85 mM per liter). These laboratory data suggested progressive acromegaly, pituitary hypersecretion of both growth hormone and prolactin, and acquired hypopituitarism with gonadal and thyroid dysfunction.

The patient's visual acuity was 20/20 vision on the right and 20/50 on the left, and the latter had deteriorated compared with the previous examination 6 months earlier. There were visual field cuts in both eyes, bitemporal hemianopsia, and a defect consistent with a chiasmatic lesion. The fundus was markedly pale, which was compatible with mild optic atrophy on the left; the right was normal.

Computed tomography showed extensive involvement of the frontal and parietal bones, orbit, maxilla, zygoma, ethmoid, pterygoid nasal septum, mandibular condyle, and coronoid process on the left. The right parietal bone was also involved. The left orbit was entirely encircled with dysplastic bone with severe narrowing of the left optic canal (Figs 2A, C, E). Magnetic resonance imaging of the sellar region revealed a large pituitary tumor compressing the optic chiasm, which was probably the cause of the bitemporal hemianopsia (Figs 2G, H).

The diagnosis was polyostotic fibrous dysplasia causing left optic nerve compression, and a pituitary adenoma secreting excess growth hormone and prolactin compressing the optic chiasm. A coronal flap was raised followed by left-side craniotomy. The left parietal and frontal bones, supraorbital rim, roof of the orbit, lateral orbital wall, and left zygoma were removed. This provided a wide exposure allowing the optic canal to be decompressed completely using curettes and rongeurs. The pituitary tumor was removed with decompression of the optic chiasm (Figs 2B, D, F). Due to extensive involvement, the resected dysplastic bones were used for reconstruction. The bones were autoclaved at 132°C and 2 atm for 5 minutes to prevent continued growth. They were remodeled and used to reconstruct the left orbit, zygoma, supraorbital rim, and left frontal and parietal areas. The involved right parietal bone was contoured with a high-speed burr.

Histologically, the resected bone showed small, thin, irregular trabeculae of woven bone lying in relatively avascular and abundant fibrous connective tissue. The pituitary adenoma consisted of uniform chromophobic and focally acidophilic epithelial cells arranged in sheets. Immunochemistry revealed diffuse reactivity for keratins and synaptophysin. Stains for chromogranin and S-100 protein were positive in some regions, and prolactin was also positive within some parts of the specimen.

The postoperative course was uneventful apart from temporary diabetes insipidus, which was controlled by desmopressin spray tapered gradually over a month. The patient's left visual acuity gradually improved and at the 6-month follow-up reached 20/40 on the left. Visual field cuts on the right had resolved completely and marked improvement was detected on the left. The autoclaved bone has retained its shape without evidence of dysplastic recurrence.

Discussion

MAS is a rare form of fibrous dysplasia with frequent craniofacial involvement. Previous studies[22] have shown that bone lesions in MAS and osteoblastic cells derived from monostotic lesions present an activated mutation of Gsα at Arginine^{201}, suggesting that the mutation in bone-forming cells may cause the abnormal bone formation in fibrous dysplastic lesions. A short fragment of the Gsα gene containing the Arginine^{201} codon was amplified with polymerase chain reaction, and mutations were identified with allele-specific oligonucleotide hybridization.[22] The somatic missense mutation in the Gsα gene in osteoblastic cells is thought to lead to increased adenylate cyclase activity, elevated cAMP levels, and increased proliferation of hormonally responsive osteoblastic cells, which results in overproduction of a disorganized collagenous matrix.[20–23] Mutations of the Gsα gene may induce abnormalities in the control of osteoblast growth and/or differentiation, resulting in fibrous dysplasia. On the other hand, the

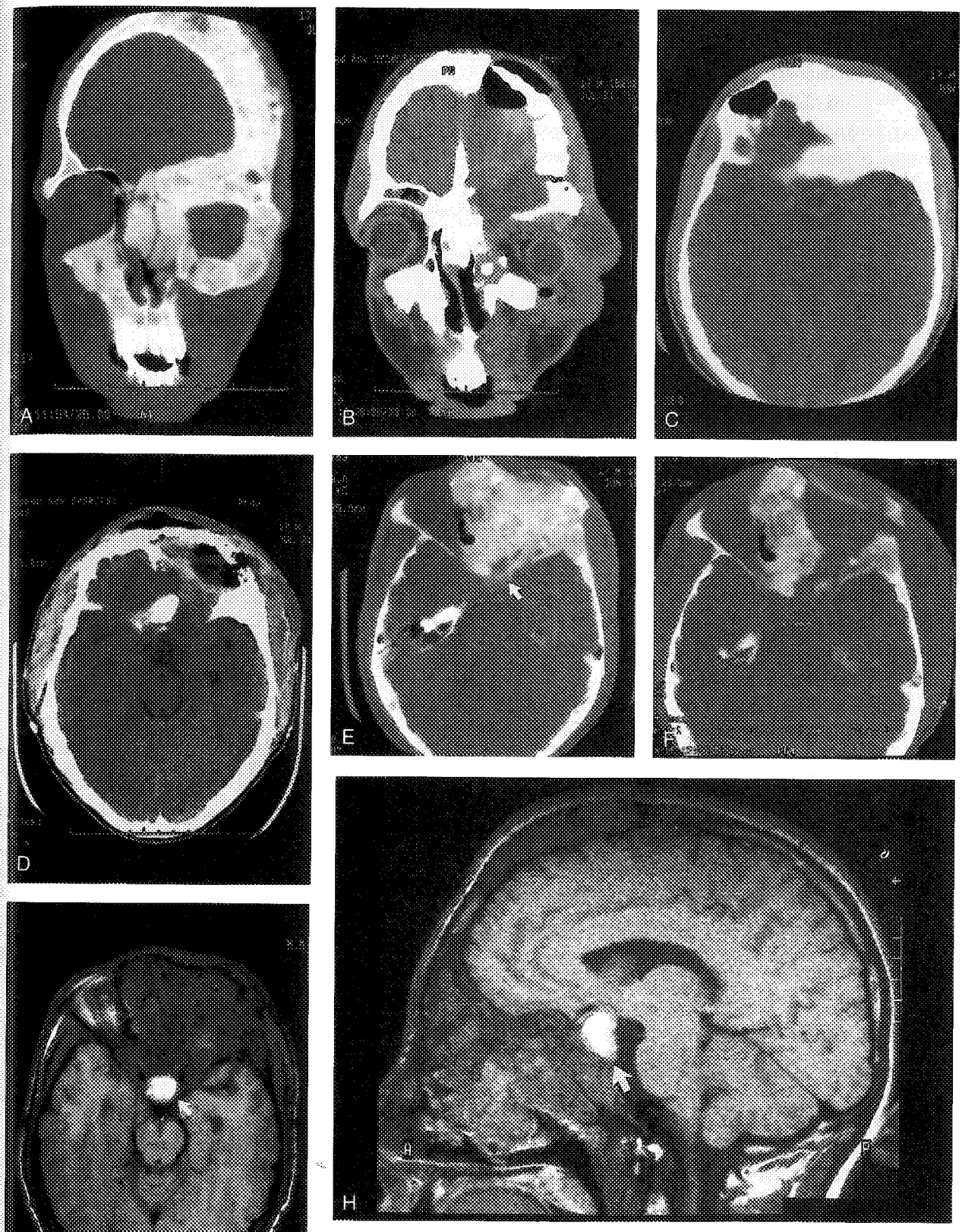

Fig 2. (A–H) Coronal (A) and axial views (C) of a computed tomographic (CT) scan demonstrate extensive fibrous dysplasia involvement of the craniofacial region. (B, D, F) Postoperative CT scans demonstrate the reconstructed craniofacial region and the optic canal. (E) Narrowed left optic canal due to dysplastic bone growth on axial CT scan (arrow). *Axial (G) and sagittal (H) T1-weighted magnetic resonance images demonstrate the pituitary adenoma* (arrow).

activation of Gsα may stimulate early immediate genes, including c-fos and c-jun, via a protein kinase A-mediated pathway, as found in pituitary cells.[37,38] In bone, the proto-oncogene c-fos seems to play a critical role in the control of normal osteoblastic cell growth and differentiation in vivo and in vitro,[39,40] and increased expression of c-fos was recently found in bone lesions in patients with fibrous dysplasia.[41] These observations suggest that the Gsα mutation may stimulate osteoblastic cell proliferation by inducing chronic stimulation of early immediate genes, which results in the overproduction of a disorganized fibrotic bone matrix.[22]

The treatment of fibrous dysplasia remains controversial. The endocrine manifestations have been treated by drugs such as octreotide, which is a long-acting somatostatin analog that has been used successfully to suppress growth hormone secretion in acromegaly, and bromocriptine—the dopamine antagonist that is used to treat hyperprolactinemia. Although no form of medical treatment has yet been proved to alter the course of the bone disease, recent studies indicate that biphosophonate therapy, pamidronate and etidronate, can alleviate pain and improve the radiological picture in fibrous dysplasia.[42] However, trials are still under way to test their effectiveness in patients with MAS.

Adequate treatment of the pituitary adenoma in MAS is difficult. Theoretically, neurosurgery is the treatment of choice, but is hazardous due to the notable vascularity of the bone lesions.[14] The therapeutic response to octreotide is promising because not only substantial reduction of GH secretion but also shrinkage of the adenoma can occur.[43] However, there are patients, such as ours, who do not show the desired response to medical treatment. Radiation therapy is not recommended because the lesion responds poorly and can change to an osteosarcoma.[29,30,35,36] However, in patients in whom surgery is contraindicated, radiation can be used.[10,44]

Surgical options include contouring or radical or near-total resection with different types of reconstruction.[45] After radical excision recurrence rarely occurs.[45,46] Usually there is no urgency to perform surgery unless there is involvement of vital structures, or severe functional or major cosmetic deformities.

Visual field abnormalities caused by pituitary adenoma or fibrous dysplasia are common, and periodic visual field examination is recommended to allow early optic nerve decompression to be performed when indicated. The early visual field disturbance is a scotoma in the periphery.[47] Optic nerve compression should be radical, but because high-speed drills may cause thermal and vibrational injury to the nerve, curettes or rongeurs are recommended.[48] The result of decompression is related to the severity of prior nerve damage and the technique used. Although results can be satisfactory, there may be no improvement in some patients.[31,49–51]

Fibrous dysplasia presents a surgical challenge. Total resection should be attempted if possible because incomplete removal is associated with 25% local recurrence.[25] The optic nerve should be decompressed carefully when indicated. Immediate reconstruction with uninvolved cranial bone grafts is recommended, but autoclaved dysplastic bones can also be used, as can contouring in selected patients.[25,50,52]

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